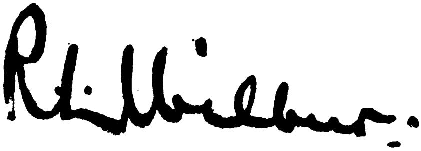
THE INFLUENCE OF PASTEUR ON MEDICAL SCIENCE

HERTER



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An Address Delivered before the Medical School of Johns Hopkins University

BY

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TO one who treasures memories of student days spent in your pathological laboratory, when each member of a small and favored group worked under the personal guidance of the great teacher whose unselfish labors have done so much for science in this country, it is indeed an exceptional privilege to address those who represent the School of Medicine that has grown since then to be the model for many an older institution. Yet I am conscious that this very privilege entails a risk,—proportioned to the

largeness of the opportunity,—of using unworthily the precious moments which fortune has bestowed on me. My choice of subject has not, I fear, lessened this hazard, for I have chosen to speak to you of one of the most significant men of the past century, whether we consider him as a person, as an investigator or as a public benefactor. I pray you, therefore, deal gently with the shortcomings of an undertaking so difficult and ambitious as that of estimating the influence of a great career on the advance of medical science.

Louis Pasteur first saw the light of day on December 27th, 1822, in an humble dwelling in the little town of Dôle in the Franche Comté. His parents had small means and limited social opportunities, but through the exercise

of forceful character and unusual fidelity to elevated ideals of life managed to give him a fair elementary education. The father, earnest, industrious and intellectually ambitious, instilled into his son the desire to become a useful and respected member of society, shielded him by constant companionship from the vulgar temptations of youth, and fired him with a love of country which a long and honorable career as a soldier of Napoleon had strongly fortified. The mother of young Pasteur was prevented by household cares from sharing closely the intellectual interests of her only son, but showed the depth of her affection by making many a little sacrifice to further his education. She was a spirited woman, possessed of lively imagination and quick intelligence, and

it is reasonably clear that the unusual artistic perceptions of Pasteur mark the perpetuation of these maternal gifts. Although the school days of Pasteur appear to have given little indication of an exceptional future, the lad showed some qualities which distinguished his work in later life. In his daily tasks, at which he worked faithfully and deliberately, he showed the most scrupulous accuracy and truthfulness, attributes which are the more noteworthy for the reason that they belonged to a temperament enriched with a strong vein of romanticism, which for a time found expression in a fervid devotion to poetic literature. Moreover, Pasteur showed while still in his teens a pronounced capacity for portraiture. During his three years of instruction at the Collège Royal

of Besançon, which he entered at eighteen years of age, the young student was more absorbed in literature and art than in science, and impressed his colleagues as being surely destined for an artistic career. The courtesy of Mr. Philip B. Marcou of Cambridge has made it possible for me to examine closely two fine examples of Pasteur's work at the end of this Besançon period. Although these portraits disclose the manual hesitancy of the imperfectly trained craftsman, they bear an unmistakable air of distinction and are executed with a respect for detail which is highly remarkable. Anyone who sees these youthful works is likely to feel that eyes so sensitive to these minutest particulars of form would be apt to see many things which others had failed to notice; and it

is noteworthy that Emil Fischer, whose calm judgment is well known, has expressed his belief that Pasteur's crystallographic discoveries were facilitated by his artistic perceptions.

The years at Besançon were followed by a highly important course of study at the Ecole Normale of Paris, during which Pasteur formed the determination to devote himself to science. For the first time in his life the gifted, impressionable young man found himself under the influence of a creative scientific mind of the highest order—a mind which has left a large and permanent mark upon the history of chemistry, and which could not fail powerfully to mould the plastic intelligence of Louis Pasteur. Jean Baptiste Dumas, who had already discovered the great principle of

substitution, united to his genius as an investigator the charm of a finished and spirited delivery. His Sorbonne lectures fairly captivated the young student and gave definite and lasting direction to his study and fancy, and, later, to his researches. Other teachers of a superior order contributed to lead Pasteur into the promising and fascinating paths of physics and chemistry. The attractive Balard, to whom bromine had first surrendered the secret of its existence, reinforced the chemical teachings of Dumas, and the admirable lectures of Delafosse aroused an enduring interest in the subtle beauty of crystalline forms. But it is to the strong intellect of Dumas that Pasteur owed his first grasp of the great principles of science and that enthusiasm for work which made it

possible to ignore the harsh and depressing material conditions that prevailed at the Ecole Normale. The recognition by young Pasteur of the importance of correlation in the physical sciences is an impressive feature of his mind at this period of close association with great chemical investigators. Evidences of this recognition exist in a singularly fine letter, full of enthusiasm for science, which he wrote to his colleague, Jules Marcou, then entering on his distinguished career as a geologist.* "Before finishing your letter," says young Pasteur, "I had already regretted that your studies in chemistry were incapable of responding to what geol-

* Mr. Philip B. Marcou has permitted me to read a large number of unpublished letters written by Pasteur to his father. The letter above quoted is dated June 10, 1845, and is one of a very small number belonging to this period.

ogy will often ask of them." . . . "I know very well that many distinguished geologists have no broad conception of chemistry, but I believe this to be a great pity, and I think that geology has not often enough turned to chemistry." The chemist of twenty-three summers held a point of view which was destined very soon to aid him in a memorable research.

It was in the field of crystallography that Pasteur, led by an interest in the ingenious and delicate methods of the science, first showed his exceptional capacity to observe minutely things and processes, and to correlate and interpret his observations. He began by carefully repeating a series of crystal measurements on tartaric acid, racemic acid, and their salts, shortly before pub-

lished by Provostaye. During the study of the recrystallized salts of tartaric acid he observed one very important but unobtrusive thing which the distinguished physicist had overlooked — regular evidences of hemihedral facets. All the tartrates showed a weak kind of isomorphism, which is apparently forced on them by the tartaric acid group, whatever other element may exist in the compound. Guided, as he tells us, first, by the observation of Biot that tartaric acid and its compound rotate the plane of polarization; secondly, by a relationship between the crystalline form of quartz and the direction of rotation ; and, finally, by Delafosse's conception that hemihedrism depends on definite crystallographic laws, Pasteur concluded that there is a relation between the hemi-

hedrism of the tartrates and their optical activity. An unexpected discovery soon proved this to be true in a conclusive and beautiful manner. One day, in the dark library of the Ecole Normale, Pasteur's eyes lighted on a remarkable paragraph from the writings of the Berlin chemist and crystallographer, Mitscherlich, relative to two different saline combinations of tartaric acid, the tartrate and the paratartrate (or racemate) of sodium and ammonium. This note stated that these two types of double salts have the same chemical composition, the same crystal form with equal angles, the same specific gravity, the same double refraction, and that in consequence of this their optical axes form the same angles. Their water solutions have the same refraction. The dissolved

tartaric acid salt rotates the plane of polarization and the racemic salt is indifferent, as had been found by Biot for the whole series of salts. "But," continues Mitscherlich, "the nature and the number of atoms, their arrangement and their distance from one another are the same in both bodies." The contradiction expressed here upset all Pasteur's physicochemical ideas and persisted for months in his mind like an interrogation point. But the day came when experience cleared up the mystery by demonstrating that there is really a difference between the tartrates and the racemates which Mitscherlich had not noticed. The former bore hemihedral facets on the right side and always rotated the plane of polarization to the right; the latter bore facets both on the right and on

the left sides and did not rotate polarized light at all. Moreover, it later appeared that this inactive racemic acid may be caused to crystallize in such a way that the crystal mass consists of equally numerous dextro-rotary and levo-rotary crystals, the former possessing hemihedral facets on the right side, the latter hemihedral facets on the left side. Both kinds of crystals were isomorphous, but the isomorphism was that of two asymmetric crystals, of an object to its reflected image. The weighty and surprising discovery had been made that indifferent racemic acid crystallizes into equal quantities of ordinary dextro-rotary tartaric acid and the newly observed levo-rotary tartaric acid.

This research on the tartrates, culminating in 1848 with the discovery of the nature of paratar-

taric or racemic acid, proved that Pasteur had already made himself master of the experimental method.

Three distinct practical results followed in the train of this research as a consequence of continued studies of crystallographic problems. In the first place there came to light numerous fresh evidences of a relation between molecular constitution, crystalline form and the property of rotating the plane of polarization. It is true that Pasteur seriously entertained some ideas of a highly speculative nature regarding the operation of dissymmetry in nature, ideas which involved him in fruitless experiments; but on the other hand the tangible and positive results of his work must be recognized as forming the basis of the modern doctrine of the asym-

metrical carbon atom, which has so illuminated our ideas of the spatial arrangements of the atoms within the molecules of organic substance; Secondly, the research on the tartrates led Pasteur to the recognition of a series of optically inactive compounds, including inactive malic acid and inactive amyl alcohol. Finally, the crystallographic researches were the bridge over which the far-seeing investigator passed on the way to lay the foundation of a new biological science, a science which has effected a veritable revolution in our conceptions of medical problems. Cagniard-Latour, Schwann and Katzing, by knowledge gained in their experiments on alcoholic fermentation, held one pass to the great secret, but saw not the fields of discovery to which it might have led them. Pasteur made his

way thither by a singularly trustworthy intuition. Greatly impressed with the circumstance that optically active substances like the sugars, the tartrates, the malates, the citrates, the gums and the proteids, seemed to be confined to the organic world and were not to be found outside the tissues of plants and animals, Pasteur made a simple yet decisive experiment. To some pure crystallized inactive ammonium paratartrate he added fermenting albuminous material. After a time the fluid was examined with the polariscope. It rotated strongly to the left. This levorotation was obviously due to the fact that the dextrorotary constituent of the paratartrate had been decomposed. An optically inactive fluid had been converted into an optically active fluid. According to

Pasteur's theoretical views this striking change indicated the mediation of living matter. The activity of unorganized purely chemical ferments could not, in his judgment, explain the facts; micro-organic life must be in some way concerned. Fortunately the mind in which this conception was born was also capable of testing its correctness by the most rigid methods of investigation. Fortunately, too, the external conditions favored a studious excursion into the processes of fermentation, for Pasteur was called in 1854 to a Professorship at Lille in a region of distilleries which involved the training of young men to proficiency in industrial chemistry, and made it essential to get new light upon the various kinds of fermentation.

At this period of Pasteur's career

the prevalent doctrines of fermentation were singularly unsatisfactory and uncontrolled by searching experimentation. The versatile Spallanzani had nearly a century before taken the important step of showing that putrescible liquids can be permanently protected from the processes of fermentation and decomposition by boiling and exclusion of air. Then Gay-Lussac, inspired by the revolutionary but constructive work of Lavoisier, made his clever attempt to show that the results of Spallanzani were due to the exclusion of the oxygen of the air from the decomposible materials, and the ingenious French cook Appert put this erroneous idea to important practical use in his widely employed method of canning perishable foods. Thus in the early days of the nineteenth century people were con-

tent to think of alcoholic fermentation as purely a chemical process. The first great blow to this widely accepted doctrine came from Theodor Schwann's incisive studies of the yeast plant in its relation to alcoholic fermentation. Very clearly did Schwann show that oxygen does not suffice to initiate the fermentation of sugar, and that the necessary condition is the presence of something which is destroyed by heat—a living organism. Unfortunately, he failed to maintain aggressively the new doctrine of the dependence of fermentation on micro-organic life. The result was that the new vitalistic hypothesis failed to make any important advance in the face of the sharp criticism and ridicule of so active and influential a teacher as Justus Liebig, whose word was nearly everywhere re-

ceived as final in matters chemical and physiological.

To Liebig and to many others it seemed a retrograde step to assume that a living organism like the yeast plant is the cause of alcoholic fermentation, for the most advanced scientific thinkers were eagerly striving to explain the phenomena of life by physical and chemical laws, and the rôle of "vital force" was being successfully restricted almost from day to day. Liebig pointed effectively to the fact that sugar undergoes other kinds of fermentation than alcoholic, such as lactic and butyric, but that nothing like a yeast organism was to be seen in these allied types of decomposition. It seemed to him that these various kinds of decomposition had one feature in common—the presence of a small quantity of nitrogenous

substance. This dead material operated as the real ferment, by communicating a kind of shock to the molecules of sugar or beef extract with which it came in contact, which resulted in the fragmentation of the molecule into smaller molecules, the essence of fermentation and putrefaction.

To Pasteur the position of Liebig was wholly unintelligible because it rested on prejudice much more than on experimental evidence. He resolved to investigate the subject of fermentations from the standpoint which he had reached by observing the fermentation of the paratartrates—that is to say, with the preconceived idea that fermentation depends on the mediation of living organisms. The first notable paper in the long series which solved one of the most pressing questions in biology

deals with lactic acid fermentation.* It might, perhaps, have been anticipated that Pasteur's first important utterance on the nature of fermentation would deal with the alcoholic form which has so great a commercial importance. He discovered, however, in lactic

* During the years 1858 and 1859 Pasteur did highly important work on alcoholic fermentation. His views as to the significance of molecular dissymmetry had already led him to regard the levo-rotary action of amyl alcohol as an indication that this regular product of alcoholic fermentation is formed by the mediation of living organisms. It was, in fact, his study of amyl alcohol (1855) together with the experiment on inactive ammonium paratartrate that incited Pasteur to undertake researches on the method of fermentative processes. His superior chemical training under Dumas was used to great advantage in all the researches on fermentation. In the case of alcoholic fermentation Pasteur showed that the acid formed is neither acetic nor lactic acid, but that succenic acid and glycerine are regular and not unimportant products. Lavoisier and Gay-Lussac represented the sugar in alcoholic fermentations as splitting wholly into alcohol and carbon dioxide, but the work of Pasteur showed that five or six per cent. of all the sugar is not decomposed in this way.

fermentation an admirable field on which to contest the ideas of Liebig and his followers, who were constantly pointing out that in lactic fermentation, so like the alcoholic form, there is nothing at all like a yeast ferment. This research ended, as is well known, in the discovery of a specific lactic acid organism or ferment, and in the cultivation of this and other organisms in an artificial medium free from albuminoids. Pasteur was not slow in forming the hypothesis that different types of fermentation are dependent on different types of micro-organisms, and this idea of specificity, soon established in relation to the ordinary decompositions, ultimately became the basis of our modern knowledge of the infectious diseases.

The research of lactic acid fer-

mentation thus gave the *coup de grâce* to the chemical theory of fermentation at the same time that it marked the birth of the promising science of bacteriology. The development of a method designed to secure pure cultures from fluid media, the use of culture media of known composition, and the careful chemical study of products of decomposition all belong to this early period of Pasteur's life, and were achievements of the deepest significance for the future of the great department of knowledge which has revivified the biological sciences.

Another research on fermentation deserves more than passing notice on account of the extraordinary discovery which appears as its almost accidental by-product. This is the investigation on butyric acid ferments (1861). This

research brought to light the fact that there are motile organisms capable of inducing a decomposition of sugar with the production of butyric acid. In the course of this research Pasteur saw that these organisms (whose motility was most puzzling on account of its suggesting animal life) behaved very differently according to their position with reference to the cover glass, those at the centre being active, while those at the periphery and exposed to the air were checked in their movements.* From this casual observation came the fundamental conception of anaerobic life. All physiologists recognize to-day "a class of beings possessing such vigorous respiratory power," as Pasteur aptly

* Pasteur fell into the error of describing the butyric acid organisms as infusorians, and thought he had shown that animal life can exist without oxygen.

says, "that they are able to live without the influence of the air by taking oxygen from certain compounds, thus occasioning in the latter a slow and progressive decomposition."

That Pasteur's original and searching examination of the problem of fermentation would one day lead him into a controversy over the unsettled question of spontaneous generation might almost have been predicted. The long discussion with Pouchet and Bastian, containing something of bitterness and not a little of the ridiculous, is a dramatic and animated chapter in the life of a peaceable but truth-loving man. As students of the influence of Pasteur on medical science we need not pause to review this controversy, for its fruits are to be found in all his subsequent work on the

specific nature of the infectious diseases. Yet this discussion, prolonged over nearly twenty years, and replete with instruction and entertainment, is worthy of a permanent place in the memories of scientific men.

After a public victory over Pouchet in 1862, which brought in its train the honor of election to the Academy of Sciences, Pasteur turned his attention toward two subjects of much practical interest which seemed closely connected with the phenomena of fermentation. One of these was the manufacture of vinegar, the other the diseases of wine. The study of vinegar led to the recognition of the micro-organic nature of the vinegar film or mycoderma, and brought acetic fermentation into line with lactic and butyric fermentations. It led also to the dis-

covery that the oxidation of alcohol through the agency of the vinegar organisms may be carried too far, acetic acid being lost by oxidation to water and carbon dioxide. Then again, Pasteur was able to aid the makers of vinegar by teaching them that the indispensable film formation can be facilitated by the actual transfer of the living ferments to the surface of the vinegar. In the study of the diseases of wine Pasteur achieved even more helpful practical results, for after recognizing the dependence of sour, bitter, and muddy wines on the presence of definite types of living ferments, he was able to suggest a simple and efficient way of controlling these disturbing agencies by the use of moderate heat. From this recommendation has sprung the use of the widely employed method of

sterilizing which we call Pasteurization.

In Pasteur's growing interest in these works of practical utility we can detect a tendency which was destined to bear rich fruitage in medical science—the inclination to employ the gifts of which he could no longer fail to be conscious in a manner likely to be directly helpful in relieving the needs of his fellow men. It was this attitude which made it possible in 1865 to lead Pasteur, not without regret, away from his studies of fermentation to a wholly new sphere of endeavor. In that year the mortality among the silkworms of northern France was so great that the silkworm industry was threatened with total extinction, and grievous famine was making its appearance in a land where comfort and contentment

had long reigned. Dumas, acting for a Senate Committee, selected Pasteur to solve the mystery of the plague. To Pasteur's remonstrance that he knew nothing of the subject and had never seen a silkworm Dumas answered: "So much the better. You will not have any ideas except those that come to you through your own observations." There were many unfriendly comments on this appointment, for some scientific men could not understand why a chemist should be chosen to cope with an obscure zoölogical problem. But Dumas knew his man and confidently relied on the great gifts he saw in him. It was quickly evident that his faith was not misplaced. Only twenty days after his arrival at Alais, Pasteur prepared a note in which he outlined a method of breeding from the

eggs of silkworms free from disease. Unlike his predecessors he made the moth the center of the efforts to regenerate the race of silkworms. "If the butterfly is sick, reject all its eggs." It required five years of Pasteur's most devoted attention, five years beset with uncertainties and disappointments, to establish this almost clairvoyant conception on an incontestable scientific basis. At the end of this period Pasteur and his highly skilled assistants had shown that there were two distinct diseases from which the silkworms died, pébrine or corpuscle disease, and flâcherie, a bacterial affection of intestinal origin. The former was proved to be a specific disease due to the psorosperm *Nosema bombycis*; the latter was believed by Pasteur to depend on a specific bacterium, but can prob-

ably be excited by several distinct varieties of bacteria. The pébrine disease, which was the chief scourge of the industry, was eradicated through the use of a careful system of breeding from eggs shown by microscopical examination, to be free from infection. The immense practical importance of this method sociologically as well as financially can be better left to the fancy than expressed in dollars and cents. But these immediate practical results do not adequately express the far-reaching effects of the great silkworm research, which marks the entry of Pasteur into the realm of animal pathology, and is thus the vestibule of modern medicine. For it is true that the laws governing the propagation and development of the flâcherie disease have the most striking analogies to those of the

diseases of man. The varying susceptibilities of different individuals to the same micro-organisms, the influence of the path of infection and the fact that flâcherie organisms acquire increased virulence after passage through the bodies of living silkworms foreshadow discoveries in human pathology. The two volumes dealing with the diseases of silkworms, and dated 1870, are works whose contents should be familiar to every independent student of the infectious diseases.

The researches on the silkworm diseases had one practical effect of considerable importance for Pasteur's later career. The success with which Pasteur had solved his intricate and widely known problem made it natural that French investigators of animal pathology should in future turn to him as the

man most likely to help them in their work, and this brought to him new opportunities for fresh successes.

It is likely that excessive work and mental stress in some degree contributed to the onset of the series of paralytic seizures which in October, 1868, threatened the life of Louis Pasteur. During the critical period of his illness many of the most distinguished scientific men of France vied with each other to share with Mme. Pasteur the privilege of nursing the man they loved so well, and of rescuing the life that had already placed science and a nation under enduring obligation, through discoveries which were either of the greatest practical utility, or appeared susceptible of almost unlimited development. Had Pasteur died in 1868 he would have left a name

immortal in the annals of science. Others would in some degree have developed his ideas. Already inspired by the researches on fermentation Lister would have continued to develop those life-saving surgical methods which will forever be associated with his name. But we may well question whether investigations in biology and medicine would not have been, for a time at least, conducted along less fruitful paths. Who shall say how soon the great principle of experimental immunity to pathogenic bacteria, the central jewel in the diadem of Pasteur's achievements, would have been brought to light?

When Pasteur recovered sufficiently to resume work it was soon clear to apprehensive friends that he had no intention of leaving his ideas to be worked out by

other men. The miseries of the Franco-Prussian war deeply affected him, and could not fail to inhibit his productiveness, but after a time the unquenchable love for experimental research was once more ascendant, and there began a new epoch, the epoch of great discoveries relating to the origin and cure or prevention of the infectious diseases of man and the domestic animals. As in the case of Ignatius Loyola, it seems as if the lamp of genius shone with a larger and more luminous flame after the onset of bodily infirmity, in defiance of the physical mechanism which is too often permitted to master the will.

The hostility of Pasteur to Germany and all things Teutonic was greatly intensified by the events of the Franco-Prussian war, and has left a somewhat regrettable

impression on his scientific work. Desiring to contribute to the rehabilitation of his unhappy country, he was led to improve the processes of brewing, with a view to increasing the wealth of France, and at the same time lessening the yearly tribute to the despised people beyond the Rhine. It was easily shown that some of the diseases of beer are due to the action of bacteria allowed to take part in the process of fermentation. But it soon became clear that the mere exclusion of these micro-organisms does not insure a brew of good beer. The problem was considerably complicated by the difficulty of deciding what constitutes excellence in beer, and this situation was not helped by the fact that Pasteur, who disliked the German drink almost as much as he disliked Germans, could not

distinguish one brew from another. Nevertheless, after many discouragements, he succeeded in establishing methods which much improved the character of French beers, methods involving the aeration of beer-wort by sterilized air, and the abandonment of open coolers. The results were far from satisfactory owing to the circumstance that Pasteur quite overlooked the part played by the undesirable forms of yeast—so called wild yeasts—in the production of abnormal fermentations. In fact it is doubtful if he could have separated the different types of yeast by the methods at his command, for even in so late a work as the famous "Etudes sur la Bière," bearing the date 1876, we are struck with the inadequate character of Pasteur's devices for obtaining pure cultures of micro-organisms.

This work, with its tender dedication to the memory of Pasteur's father, was a highly important contribution to bacteriology in spite of its many botanical defects. It is really a bacteriological potpourri bringing together the writer's views on many questions, rather than a strict treatise on the diseases of beer. Besides chapters on the causes of bad beer and improved methods of brewing, the volume treats of the origin of ferments and furnishes conclusive experimental evidence against that plastic doctrine of the transformation of species around which the friends of the spontaneous generation fallacy were hopefully rallying. But by far the most striking and original chapter in this notable volume is that in which Pasteur formulated his physiological theory of fermenta-

tion—the startling theory that the essential characteristic of fermentation is life without air, life without free oxygen. This theory, if not entirely upheld by other biologists, has at least proved a powerful stimulus to new studies of this unexplored aspect of life.

Pasteur's life was prolonged a quarter of a century after the close of the war with Germany, and during a large part of this long period his mind dwelt almost unceasingly on two phases of the great biological and practical problems which it was his fortune to develop so fruitfully. One of these was the investigation of the etiology of disease as related to the activity of micro-organisms. The other was the experimental study of the amazing phenomena of immunity to the action of specific viruses or virulent micro-

organisms. These two affiliated phases of bacteriological research culminated in one of the most remarkable discoveries of all time —remarkable for its practical results, but even more striking as an example of the use of the imagination in science. It is well worth while to consider the chief events that ultimately led to the discovery of a method of immunization against the virus of hydrophobia.

The idea that some diseases are due to living micro-organisms was suggested by Boyle two hundred years before the days of bacteriology. From time to time thoughtful men took up this idea as worthy of discussion, but it received no substantial confirmation until Schoenlein, with the aid of the microscope, made his admirable discovery of the infectious

nature of ring worm. This was in 1839. Within a few years Henle, the gifted anatomist of Göttingen, proposed an ingenious explanation of the infectious diseases which assumed the agency of micro-organisms, but the theory, though based on thoughtful clinical considerations, was deficient in experimental data and had little practical influence on medicine. It is scarcely surprising that the leading scientific minds of the epoch should have been hostile to any mere hypothesis of contagion by germs, for in their struggle against the ancient conception of a vital force they regarded the idea of a *contagium vivum* exactly as Liebig had regarded Schwann's and Pasteur's doctrine of fermentation. Even the illuminating-cell doctrine of Virchow was not especially favorable to the idea that

living organisms from outside can excite disease by fixing themselves and developing in the body. Pasteur's training and temperament and genius admirably fitted him not merely to detect the great central truth of etiology, but to force it, in spite of stubborn opposition, upon a doubting world half stunned at the boldness of the new doctrine. But while he took a large part in compelling this revolution in the conception of disease, the way was prepared by others, and especially by the fine observations of the biologist, Casimir Joseph Davaine, and the accurate and ingenious experimental methods of Robert Koch.

Davaine, while assisting the clinician, Rayer, in the study of the devastating anthrax plague in 1850, observed little thread-like

bodies in the blood of animals dead of this disease. Ten years later Delafond observed these little threads to be living organisms with the power of multiplying outside the body. Thirteen years after his first observations, Davaine, incited by Pasteur's suggestive work on the butyric acid ferment, reopened his study of anthrax and confidently proclaimed that the organisms he had found were the cause and the only cause of anthrax. But it required the superior technique of Koch, unquestionably, to obtain the anthrax organisms in pure culture, to follow the cycle of their development in the animal body, and thus to place the important discovery of Davaine on an impregnable scientific foundation. Pasteur, entering this field a little later, independently

worked out some of the most striking features of the etiology of anthrax, and convinced the best scientific minds of France of the relationship between the bacilli of Davaine and the perpetuation of the anthrax plague.

Very closely associated with Pasteur's work on anthrax is the admirable research in which the master, aided by Joubert and Chamberland, discovered the organism known to us as the bacillus of malignant oedema, but described by its detectors as the vibrio septique, in the same year (1877) in which the well-known publication on anthrax appeared. Of the many excellent features for which this research is distinguished there are two that deserve especial mention. First, the recognition of the septic vibrio in the blood of animals not

newly dead of anthrax was an extremely important service in clearing up the gravest objections to Davaine's doctrine of the etiology of anthrax. Secondly, the observation that the septic vibrio is anaerobic affords the earliest example of a pathogenic organism which in its vegetative form is inhibited by the presence of oxygen—a discovery which we may reasonably attribute to the experience gained sixteen years before with the butyric ferment.

In looking for fresh proofs of the bacterial origin of disease, Pasteur made some visits to the hospitals of Paris, and thus came into closer relations with the practitioners of medicine and surgery. The alert and intellectually honest minds bade him welcome and gave him every help to pursue his studies; the conservatives

looked at him askance, confidently set up their time-worn theories against his experimental proofs, and lost no occasion to ridicule the germ theory of the origin of disease. To-day it is difficult for us to picture the incredulity and amazement of many prosperous and self-satisfied practitioners on hearing Pasteur's announcement that he had found the same pus-exciting micro-organisms (probably the staphylococcus pyogenes aureus) in the pus from a series of boils and in the pus from osteomyelitis, and that these conditions, so different in clinical character, are identical as regards etiology. Very soon a second bomb of the same nature fell into the conservative camp, with the confident and even fervid declaration that child-bed fever is a septicaemia commonly due to a

coccus in chains (streptococcus),* which could be detected in the cavity of the uterus, in the blood of the uterine sinuses, and in the blood of living patients. The far-reaching practical results of this investigation, to which Pasteur devoted only one short publication, are so well known to you that they call for no comment here.

Not long after the beginning of the anthrax study the attention of Pasteur was directed to a disease which was destined to play a remarkable part in leading to the great goal toward which the researches of the master were carrying him—the discovery that it is possible experimentally to

* Pasteur's description of the organism found in puerperal septicaemia is not enough to make it certain that he was dealing with pure cultures of the streptococcus pyogenes.

ıduce immunity to disease caused y virulent micro-organisms. Perɔncito of Turin and Toussaint of oulouse had reached the conusion that an organism detected y the former is the cause of ıicken cholera, but neither had ıe requisite bacteriological traing actually to establish the corctness of this contention. Paseur was consulted on the subject, and, bringing to bear his superior knowledge and technical skill, succeeded in growing the organism outside the animal body and in experimentally inducing chicken cholera by means of these cultures grown *in vitro*. Returning to the laboratory after a short absence, he found that his cultures of the bacilli of chicken cholera had failed to grow or had grown only feebly. To increase the activity of these micro-organisms,

they were now inoculated into normal fowls—a procedure suggested by previous experiments with other bacteria. The results were disappointing, for the inoculated animals showed no signs of the disease. This made it necessary to isolate and grow actively pathogenic bacteria from animals with chicken cholera. Having done this, it occurred to Pasteur that it would be of interest to inoculate with fresh and virulent bacilli the animals already treated with the attenuated strain of chicken cholera organisms. This was done without delay, and to his surprise nearly all of these prepared animals resisted the virulent germs. They had been immunized by means of the attenuated cultures and a new principle had come into medicine. By experimental study and long re-

flection on the work of Jenner, the mind of Pasteur had been prepared to grasp the immense practical significance of this discovery. It appeared probable that what had been accomplished for chicken cholera could be extended to other diseases. One special consideration made Pasteur feel hopeful as to the possibility of immunizing sheep and cattle against anthrax. He had noticed that certain sheep long exposed to anthrax through grazing on infected pastures did not die after experimental inoculation with a virulent anthrax culture, whereas previously unexposed animals of the same herd died promptly after such inoculation. Moreover, he knew from experience that fowls can be immunized against chicken cholera by feeding them the specific germs of that disease, and

this fact strongly suggested a similar explanation for the anthrax immunity which he had noticed. With this analogy in mind, Pasteur took the first step toward the preparation of a vaccine against anthrax. As in the case of chicken cholera, he strove to attenuate the specific organisms of the disease. This he tried to do in the way that had succeeded so well in the case of chicken cholera—that is, by exposing anthrax cultures to an abundance of oxygen at the body temperatures. But Pasteur found that under these conditions the anthrax organisms retain their virulence, owing, he believed, to their capacity to produce resistant spores. To check this growth of the anthrax spores he successfully resorted to the procedure of growing his cultures at a temperature of 42°—43° C.

in the presence of oxygen. By varying the procedure somewhat he was able to prepare a series of anthrax vaccines of different degrees of activity, the use of a mild vaccine being followed by that of a stronger one in the course of immunization.

The announcement by Pasteur, Chamberland and Roux of a method of protecting animals against the anthrax scourge excited great public interest, but was in many quarters received with skepticism and derision. Pasteur was invited to make a large-scale public test of his claims near Melun, at the farm of Pouilly-le-Fort. He accepted the challenge gladly, and on May 5, 1881, began a series of public inoculations which will always be memorable in the annals of medical science. The publicity with which

the unique experiment was performed, the unconcealed hostility and suspicion of many of the onlookers, and the alternating hopes and fears of Pasteur, have been most entertainingly described by M. Vallery-Radot. The outcome was a convincing demonstration of the practicability of Pasteur's method of immunizing against anthrax in sheep. Nevertheless, two years later, in an ill-natured attack on Pasteur's work, Koch attributed the discovery of vaccination against anthrax to Toussaint, and pointed to a paper in which the latter had reported some experiments describing the immunization of dogs and sheep by means of anthrax bacilli which had been heated at 55° C. for ten minutes.

While it is true that Toussaint thus immunized animals against virulent anthrax organisms, his

method of obtaining a vaccine was unreliable and unsuited for practical use. The fact is that Toussaint, stimulated by Pasteur's discovery of a method for immunizing against chicken cholera, prepared a vaccine which sometimes protected against the disease, but which was dangerous, owing to uncertainty as to the number and condition of the living anthrax organisms which it contained. His publication appeared six months after that of Pasteur, who, although greatly interested in the observation of Toussaint, criticised the methods of the latter and ultimately prepared a safe vaccine consisting of definitely attenuated anthrax organisms. The crude experiments of Toussaint were wholly based on the epoch-making immunization to chicken cholera.

On March 15, 1882, Louis Thuillier, the earnest and gifted but ill-fated young assistant of Pasteur, discovered in the blood of swine dead of erysipelas (rouget de porc) an organism which appeared to be the active agent of this plague—an organism which Klein in his elaborate investigation had quite overlooked, but which was independently discovered by Detmers of Chicago. Pasteur had inspired this fine research of Thuillier and stood ready to develop it. By carrying the suspected organism through many generations on veal bouillon, and finally introducing it into hogs, the true swine erysipelas was readily induced. The real problem, however, was to make an attenuated virus for the purpose of immunizing against the disease. Pasteur succeeded in ob-

taining a virus capable of protecting certain races of hogs for a period of a year or more, and this important practical success is rendered especially noteworthy by the method that was followed in attenuating the rouget organisms. In 1887 he had found in the saliva of rabid dogs an organism highly virulent for rabbits (micrococcus of rabbit septicaemia).* Adult guinea pigs were immune, but young guinea pigs quickly died after inoculation. By passing the organism through a series of young guinea pigs it gained in virulence until it grew fatal for adult guinea pigs. But the modification which especially impressed Pasteur was that the bacteria which had thus gained in pathogenic qualities for guinea

* Micrococcus lanceolatus.

pigs had at the same time become attenuated for rabbits.

The memory of this singular observation now came to his aid in the rouget research. After passing the rouget bacteria through a series of pigeons (which are naturally susceptible), it was found that the blood from the last pigeon had become much more pathogenic for swine than blood from hogs dead of swine erysipelas. On the other hand, Pasteur discovered that while the passage of the rouget organisms through a series of rabbits (which are not naturally susceptible) permitted these bacteria to grow more readily in the blood of rabbits and to become more highly pathogenic for them, they became definitely and permanently diminished in virulence for swine. Thus, after inoculation with modified organ-

isms, hogs became ill, but did not die. On their recovery they were immune to fatal rouget. The genius of Pasteur thus gave to biological science a definite method of permanently modifying the pathogenic characters of certain micro-organisms. This contribution is recorded in a paper which won the applause of the Academy of Medicine, and which even to-day excites admiration for its mingling of experimental skill and scientific imagination.

So far back as 1880, in the midst of the exacting anthrax investigation, Pasteur had found time to begin a new research on the protective action of attenuated virus. From modest beginnings this research grew in the hands of the master to be the crowning work of his life, in the sense of embodying the fullest and in some

respects most original expression of his ideas on the use of experimentally enfeebled viruses for the mitigation of infectious processes. The transmission of rabies through bites made probable the infectious nature of the disease and encouraged a hope that it would not be very difficult to isolate the specific organism from the saliva of rabid dogs. But the most systematic efforts to isolate such an agent were rewarded only by failure. To this disappointment was added a second, even more disconcerting. It was found that the experimental transmission of the disease by means of saliva is a matter of great uncertainty. Moreover, the uniformly fatal outcome of hydrophobia made it impossible to form any opinion as to whether the unknown virus was capable of conferring immunity.

Many an investigator would have been deterred from the prosecution of an enterprise so unpromising, but the interest of Pasteur had been fully enlisted before he realized the difficulties of the problem, and the tenacity of his nature urged him to keep patiently on his course. He saw clearly that a reliable way must be found to communicate rabies experimentally, and acting on a suggestion made by Dr. Dubue of Pau, that the disease is essentially one of the central nervous system, Pasteur took small bits of nervous tissue from animals dead of rabies and placed them under the skin of experimental animals. This method was no considerable improvement on similar inoculations of saliva from rabid dogs, but it served as the clew to a notable advance. This

was the introduction of rabic nerve-tissue directly into the central nervous system of the animal to be infected, a procedure based on the idea that since rabies behaves like a disease of the nervous system the micro-organisms causing it would be likely to find in the nervous system a living culture medium highly favorable to their growth. The acute intelligence of the masterful experimentalist is strikingly illustrated by the fact that failure to isolate specific micro-organisms had not shaken his faith in the testworthiness of his preconceived idea. Hence, when he found that hydrophobia regularly followed subdural inoculation with rabic nervous material, he was more pleased than surprised. The first dog thus inoculated showed unmistakable signs of rabies after fourteen days,

and other animals gave similar results. Moreover, on bringing into practice the experience he had gained in studying swine erysipelas, Pasteur found that he could increase the pathogenic properties of the virus by carrying it subdurally through a series of rabbits or reduce it for dogs by carrying it subdurally through a series of monkeys. He thus had at his command three different viruses — a virus of natural strength, a virus of increased virulence and an attenuated virus. Later experiments showed that a safer virus could be prepared by drying over caustic potash, at 21° C., the spinal cords of rabbits dead of rabies.

By injecting subcutaneously first a weak virus and subsequently a stronger one into parts with very few nervous structures,

Pasteur succeeded in immunizing dogs against otherwise fatal subdural inoculations. This success suggested the possibility of immunizing human beings. The relatively long duration of the period of incubation, which is commonly about forty days, made the outlook for human immunization peculiarly promising. The opportunity for trying the method soon appeared in the person of the little Alsatian lad Joseph Meister, who came to Paris with fourteen wounds inflicted by a rabid dog. Pasteur courageously resolved to make an effort to rescue the bitten child from the certain death to which he was doomed, by making successive injections of rabbit viruses of increasing strength. The result is known to all the world ; the effort to utilize the long period of incubation quickly to establish im-

munity through repeated inoculations, proved a success, not only in the case of little Meister, but in many thousand other instances.

The great research on rabies fittingly marks the culmination of Pasteur's long career as an investigator. In that investigation can be seen the same technical skill, the same respect for minute detail, and the same pertinacity that had distinguished so many earlier researches, but there can be seen also a degree of originality and a fertility of resource that excel nearly all previous exhibitions of these powers. The accumulated experience of a quarter century of original study of micro-organic life served as liquid intellectual capital on which Pasteur drew for guidance at every turn in the extraordinarily intricate and perplexing study of rabies. And it seems

wholly clear that this new discovery could never have been made without such a treasure of experimental experience.

One who looks only at the results of Pasteur's far-reaching work is apt to overlook his mistakes and shortcomings, and to forget that he made some serious errors not only in the interpretation of experimental data, but sometimes also in experimental technic. To pathologists of the present day Pasteur's conception of acquired immunity appears so crude that it is difficult to believe he ever entertained it seriously. His work on chicken cholera naturally led him to form a theory to account for the immunization which he observed, and this theory was that immunity arises from the inability of a pathogenic organism to grow in a medium in

which it has previously developed. Animals thus become immune because the necessary nutrient material for the multiplication of the specific organisms has been used up, just as an organism will after a time cease to grow in vitro in an old culture medium. It seems strange that he did not test this theory by trying to grow the organisms outside the body in the blood and serum of both the immunized and normal animals, and so learn that he was in error. The short and usually inadequate descriptions of micro-organisms which Pasteur has given in his terse publications have aroused much criticism from bacteriologists, and it cannot be denied that he underrated the importance of minute morphological and cultural studies—studies without which some of the most important mod-

ern advances could not have been made. Nor is it easy to explain the reluctance with which he adopted the improved bacteriological technique of other investigators. Koch's method of plating bacteria, Weigert's and Ehrlich's methods of staining and certain important nutrient media found their way into his laboratory only after long delay, and through the efforts of assistants. Pasteur's comparatively faulty technique for obtaining pure cultures of bacteria is doubtless responsible for many of the disheartening results reported by foreign observers who used his vaccines. Nevertheless his methods in the main served their purpose well, and we should remember that the most finished instruments cannot belong to the pioneer who makes his own tools. Fortunately Pasteur was greatly

favored by the circumstance that in many of his etiological studies he made cultures from the blood, where the specific micro-organisms often existed in pure culture.

Although even the plainest narrative of Pasteur's individual achievements is proof enough that his work holds a unique position in the history of biological science, it is worth while to consider in more general terms what it was that the consummate experimentalist added to the science of medicine. Such a consideration gives us a more just measure of his influence than the most detailed recital of specific investigations. If we would understand the influence of Pasteur on medical science we must recognize that his example as the apostle of an almost untried method of approaching the

problems of medicine has been no less enlightening than his actual discoveries. Emerson has said: "Great men exist that there may be greater men." The recent history of medicine in the United States as well as in Europe, plainly shows that the seed of example sown by Pasteur has already fallen on receptive soil, from which have sprung new combinations of human faculties powerful for the amelioration of human life. Our country has no greater cause for satisfaction than the knowledge that the ideality as well as the methods of Pasteur, has inspired a growing circle of original investigators in medical science who labor for the common welfare. Let us hope that this circle will be continually widened, in the future as in the past, by accessions from the students of this University,

where the best ideals of work have been so richly nurtured.

Perhaps the most deeply significant feature of Pasteur's contributions to medicine is their direct dependence on the principles of physics and chemistry, the sciences that so often lie at the heart of real advances in biology. Medical men trained along the conventional semi-scholastic lines had often dabbled with these fundamental sciences, and sometimes the superficial contact had yielded creditable or even important results. In many instances, also, truly great advances had come from the labors of men who like Malpighi, Bichat and Johannes Müller were wide awake to the fact that sound medicine must rest on sound biological conceptions.

But despite the activity of numerous gifted medical men of

broad scientific sympathies, the medical profession at the beginning of Pasteur's career was dully following a well trodden but nearly blind road, in the hopeless struggle to solve the intricate problems of human pathology and physiology by minute observations and experiments confined largely to the most complex representatives of animal life. Then for the first time there appeared in the biological sciences a man profoundly trained in the methods of chemistry and physics, and inspired, moreover, with a firm confidence in the applicability of these sciences to the solution of biological and medical problems. Triply armed with a sound method, a lofty imagination, and a strong will to serve his country, Louis Pasteur entered the wide arena of medical research, to win there the

triumphs that have reconstituted medicine, and have secured him an undying fame. Step by step, with rigid logic and unfaltering determination, he passed from the early crystallographic discoveries to the new conception of fermentation, and from this to the crucial discoveries relative to etiology and immunity for which the medical sciences had waited so long.

To have fought the long battle of life with unwavering constancy to the loftiest ideals of conduct, toiling incessantly without a thought of selfish gain; to have remained unspoiled by success and unembittered by opposition and adversity; to have won from nature some of her most precious and covert secrets, turning them to use for the mitigation of human suffering:—these are proofs of rare qualities of heart and mind.

Such full success in life did Louis Pasteur attain, and from the consciousness of good achieved, his noble nature found full reward for all his labor.

Of the children whom fortune has endowed with splendid gifts, there are few whose lives have affected so profoundly and so beneficently the fate of their fellows, few who have earned in equal degree the gratitude and reverence of all civilized men. Although not many can hope to enrich science with new principles, all of us may gain from Pasteur's life the inspiration to cultivate the best that is in us. Let us keep living in our memories the inspiriting words which the master spoke on the seventieth anniversary of his birthday: "Young men, young men, devote yourselves to those sure and powerful

methods, of which we as yet know only the first secrets. And I say to all of you whatever may be your career, never permit yourselves to be overcome by degrading and unfruitful scepticism. Neither permit the hours of sadness which come upon a nation to discourage you. Live in the serene peace of your laboratories and your libraries. First ask yourselves, what have I done for my education? Then as you advance in life, what have I done for my country? So that some day that supreme happiness may come to you, the consciousness of having contributed in some manner to the progress and welfare of humanity. But, whether our efforts in life meet with success or failure, let us be able to say when we near the great goal, 'I have done what I could.'"

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